



These projects have received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 963845 (ONTOX), No. 965406 (PrecisionTox), No. 964537 (RISK-HUNT3R)

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Open **2-3 July 2026** Symposium

Maastricht
The Netherlands

Quantitative assessments of population-level susceptibility to toxicity: relevance to humans and wildlife

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Author's affiliation: Misvik Biology

Project: PrecisionTox



- To assess the impact of genetic variation on toxicity using a human genome diversity cell line panel
- To identify genetic variants (SNPs) and affected cellular mechanisms associated with toxic responses
- To compare the identified human mechanisms to mechanisms identified from *Drosophila Melanogaster* to enable human toxicity assessment in non-scientist species

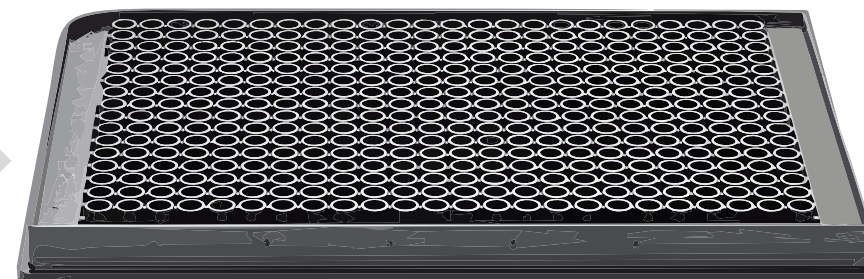
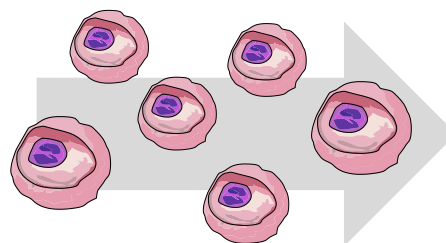


Chemical selection screen; 91 chemicals, 20 LCL's

Select 13 with the highest variation; CADMIUM CHLORIDE, SODIUM (META) ARSENITE, ACRYLAMIDE, 4-METHYL IMIDAZOLE, GENISTEIN, DEXAMETHASONE, VALPROIC ACID, TAMOXIFEN, CYCLOSPORIN A, ROTENONE, DISULFIRAM, 5-FLUOROURACIL, (+DMSO)

Main screen; 13 chemicals, 261 Lymphoblastoid cell lines, 4 biological replicates, 2 viability endpoints, 8 concentrations

Anova, GWAS, Pathway analysis





The Human Lymphoblastoid Cell Line Panel

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EUROPEAN

FIN – FINNISH

GBR – BRITISH

IBS – IBERIAN IN SPAIN

EAST ASIAN

CHS – HAN CHINESE SOUTH, CHINA

CDX – CHINESE DAI IN XISHUANGBANNA

KHV – KINH IN HO CHI MINH CITY, VIETNAM

SOUTH ASIAN

STU – SRI LANKAN TAMIL IN THE UK

PJL – PUNJABI IN LAHORE, PAKISTAN

BEB – BENGALI IN BANGLADESH

AMERICAN

PEL – PERUVIAN IN LIMA, PERU

MXL – MEXICAN ANCESTRY IN CALIFORNIA, USA

CLM – COLOMBIAN IN MEDELLIN

PUR – PUERTO RICAN IN PUERTO RICO

AFRICAN

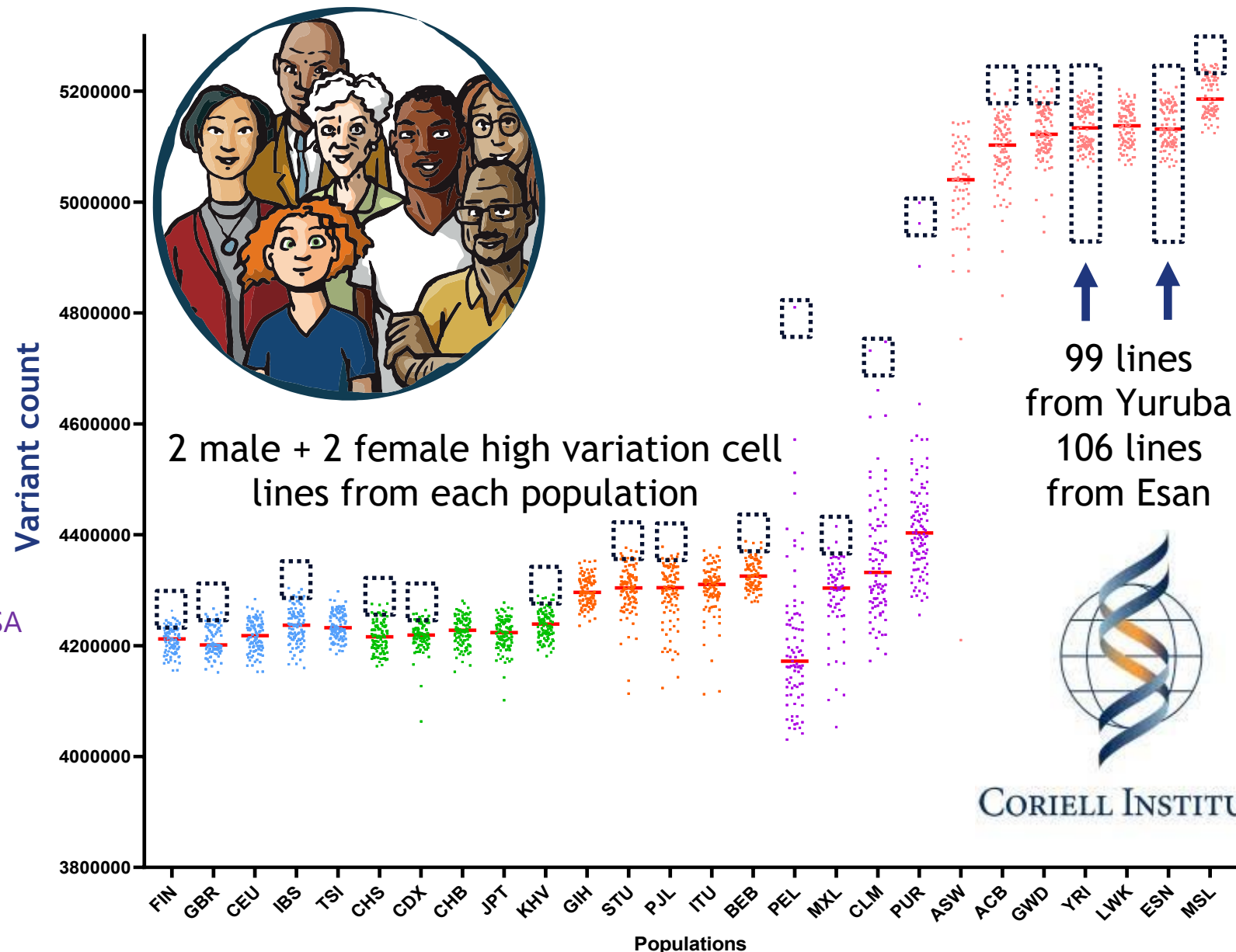
ACB – AFRICAN CARIBBEAN IN BARBADOS

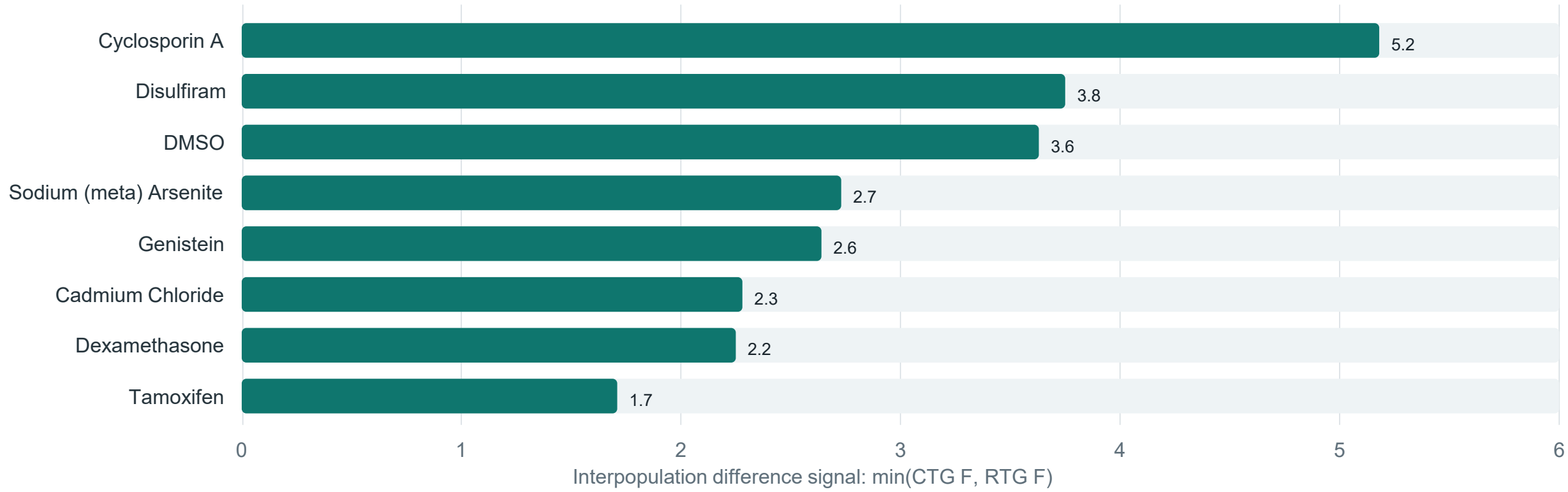
GWD – GAMBIAN IN WESTERN DIVISION -
MANDINKA

YRI – YORUBA IN IBADAN, NIGERIA

ESN – ESAN IN NIGERIA

MSI – MENDE IN SIERRA LEONE

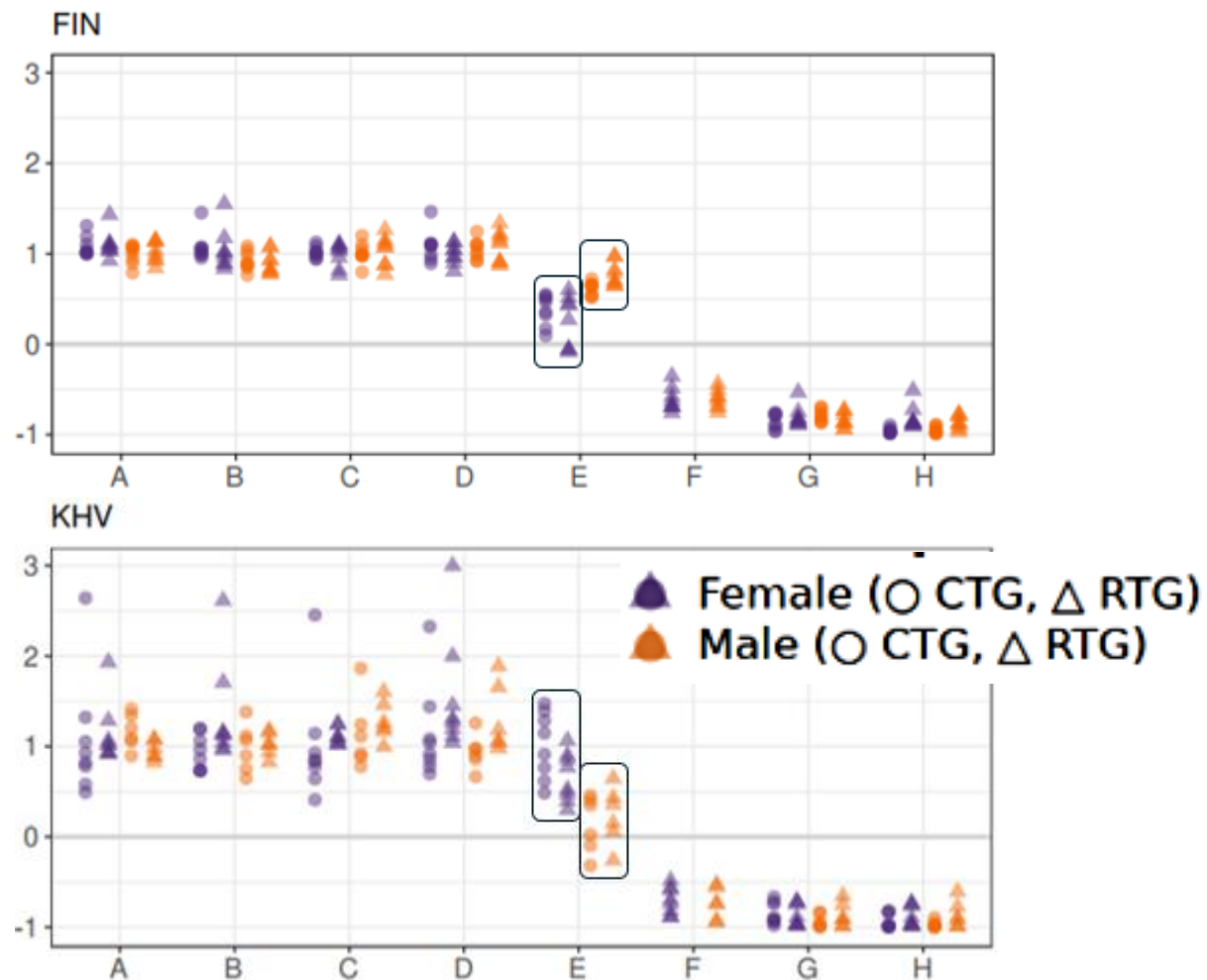




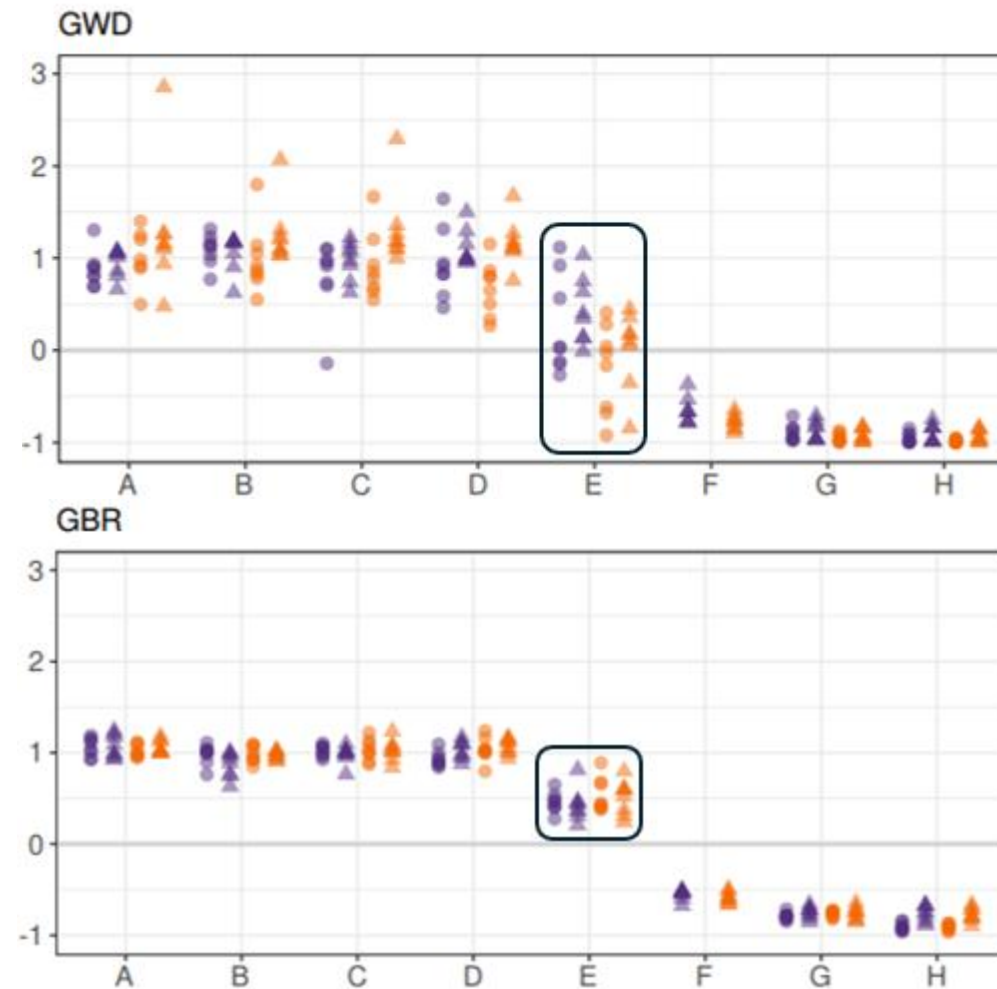
Chemicals with response differences between populations

Bars are ranked by the smaller population F-statistic across both CTG and RTG assays. Longer bars indicate stronger interpopulation variability

Sex differences; Finnish females are more sensitive than males. Opposite is true for Vietnamese.



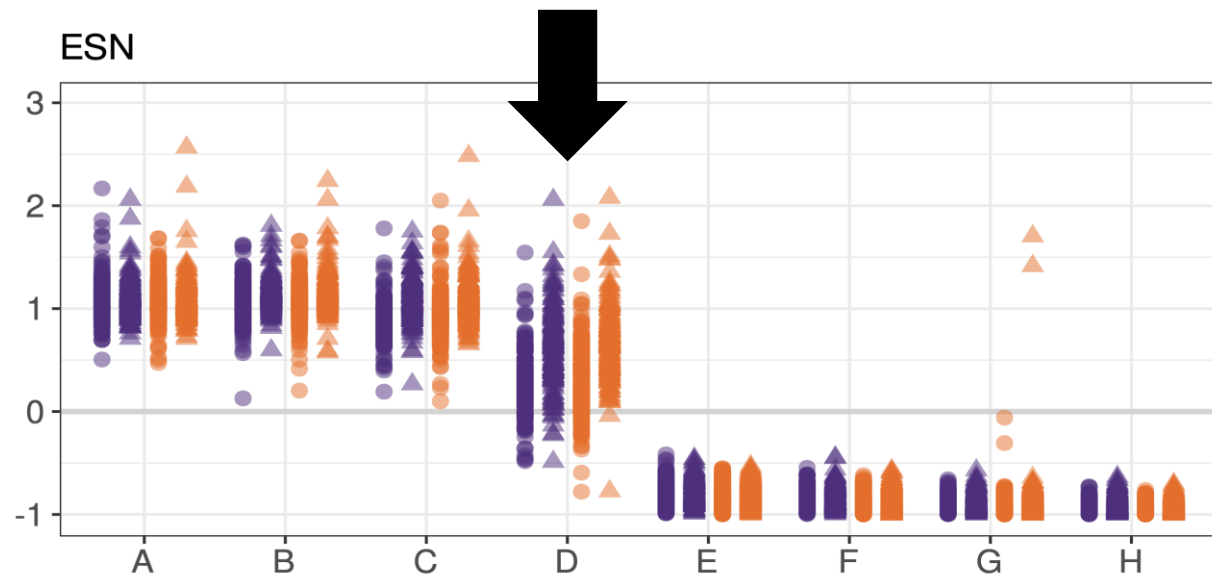
Population differences; Gambian are more sensitive than British





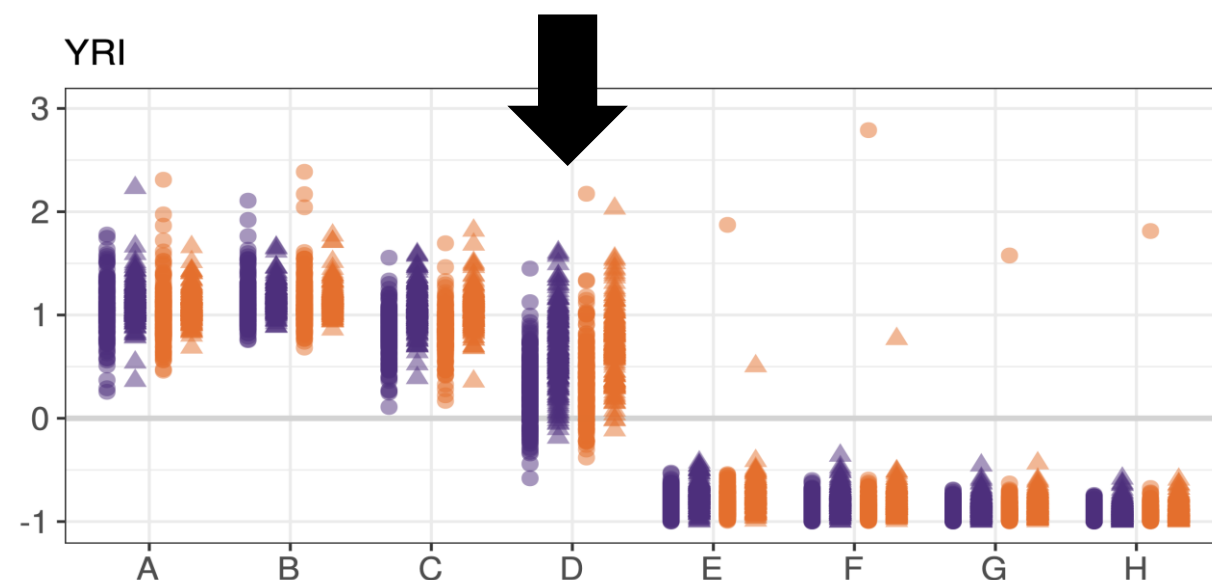
GWA; Variation in Sensitivity to Cadmium Chloride Across Esan and Yoruba Populations

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GWAS focused on the two Nigerian populations to gain adequate sample size and statistical power for further analyses.

ESN = Esan
YRI = Yoruba

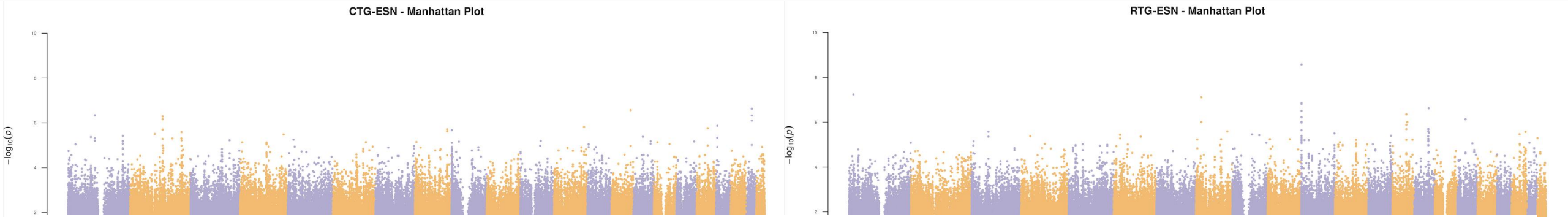


Concentration (mM)

A: 3.494×10^{-4}
B: 1.747×10^{-3}
C: 8.734×10^{-3}
D: 4.367×10^{-2}
E: 2.184×10^{-1}
F: 1.092×10^0
G: 5.459×10^0
H: 2.729×10^1

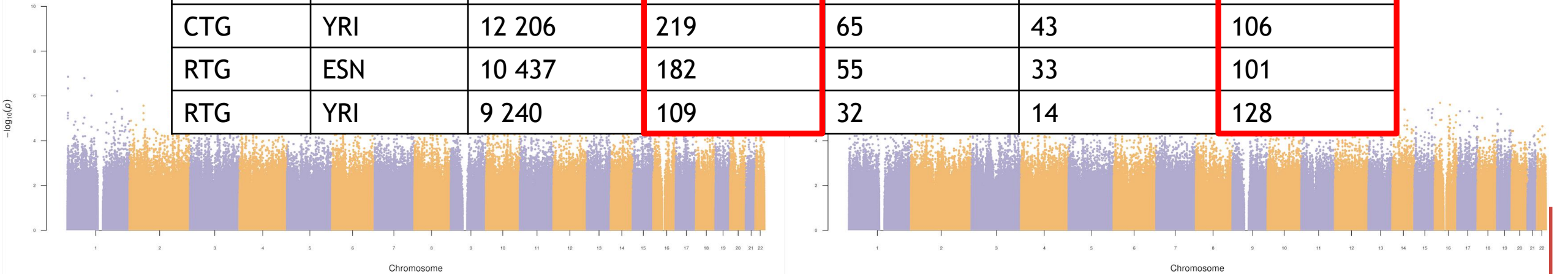
Sex x Endpoint

Female (○ CTG, △ RTG)
Male (○ CTG, △ RTG)



Single-nucleotide polymorphisms (SNPs) with $p < 1 \times 10^{-5}$ mapped to nearby or overlapping genes, enabling biological interpretation of association signals.

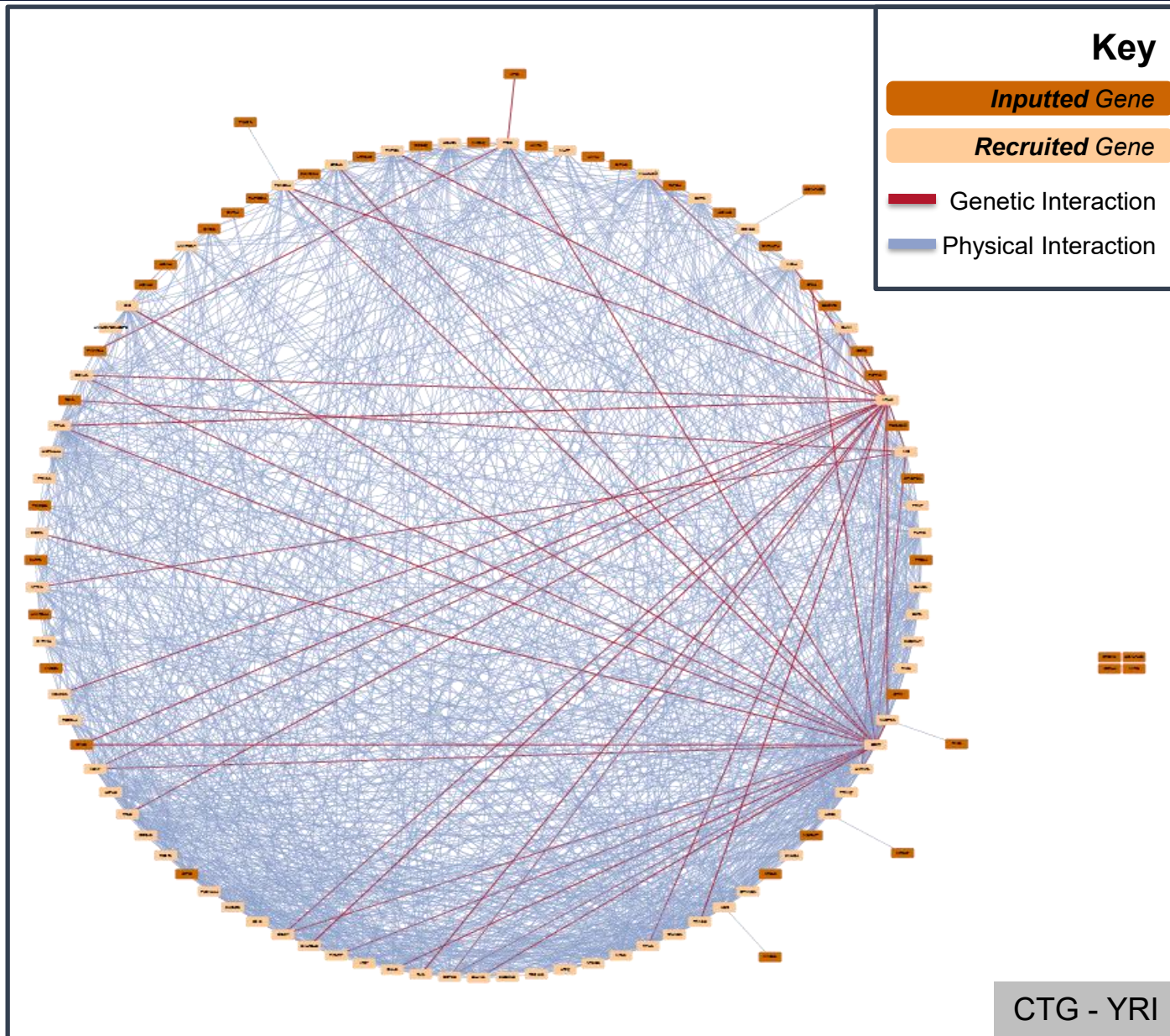
Endpoint	Population	Unique SNPs $p < 0.001$	Unique SNPs $p < 0.00001$	Unique Genes $p < 0.00001$	Unique Genes Network Input Set	Total Genes In Network
CTG	ESN	10 671	85	21	12	17
CTG	YRI	12 206	219	65	43	106
RTG	ESN	10 437	182	55	33	101
RTG	YRI	9 240	109	32	14	128



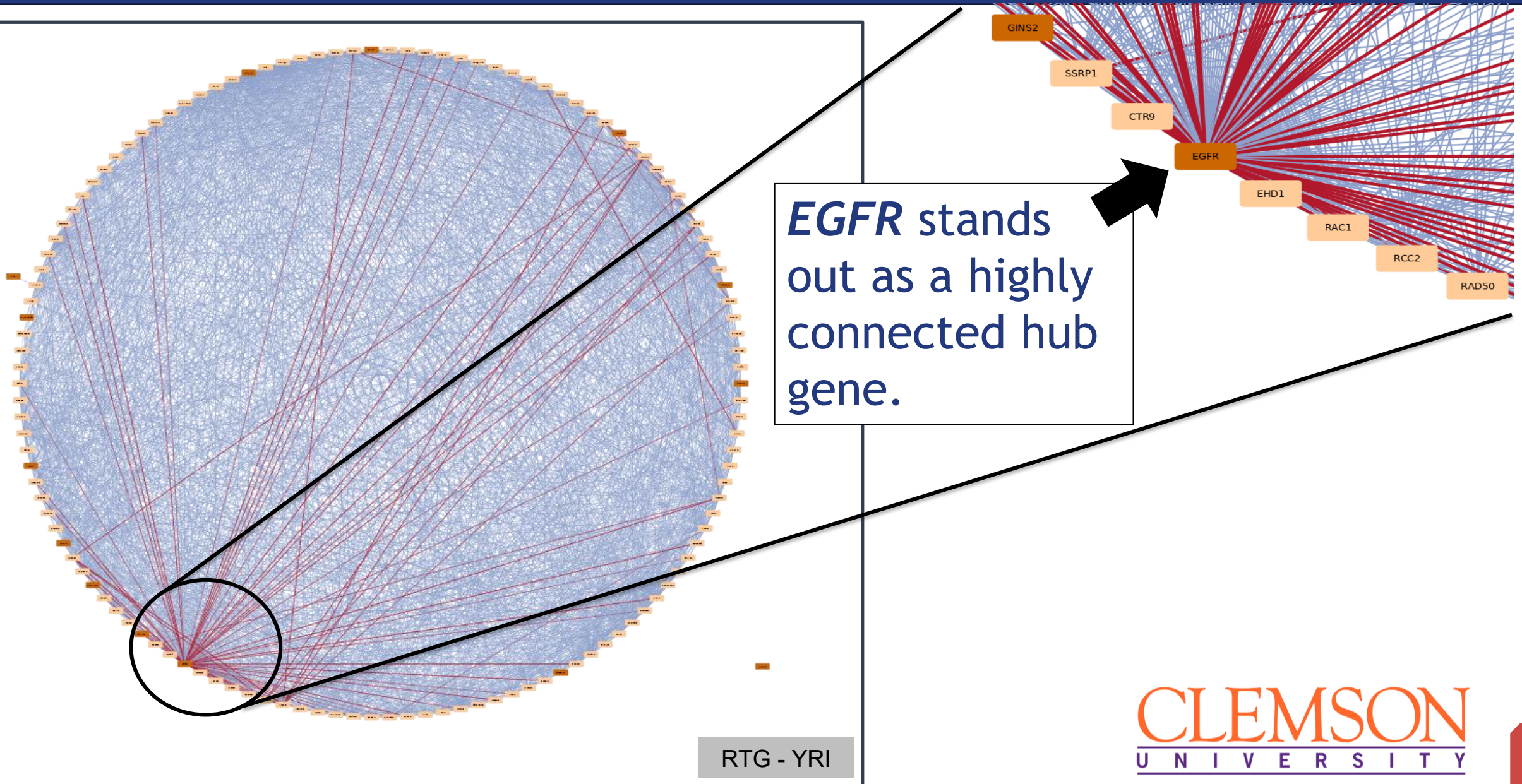


GWA; Interaction Network of Genes Associated with Exposure to Cadmium Chloride

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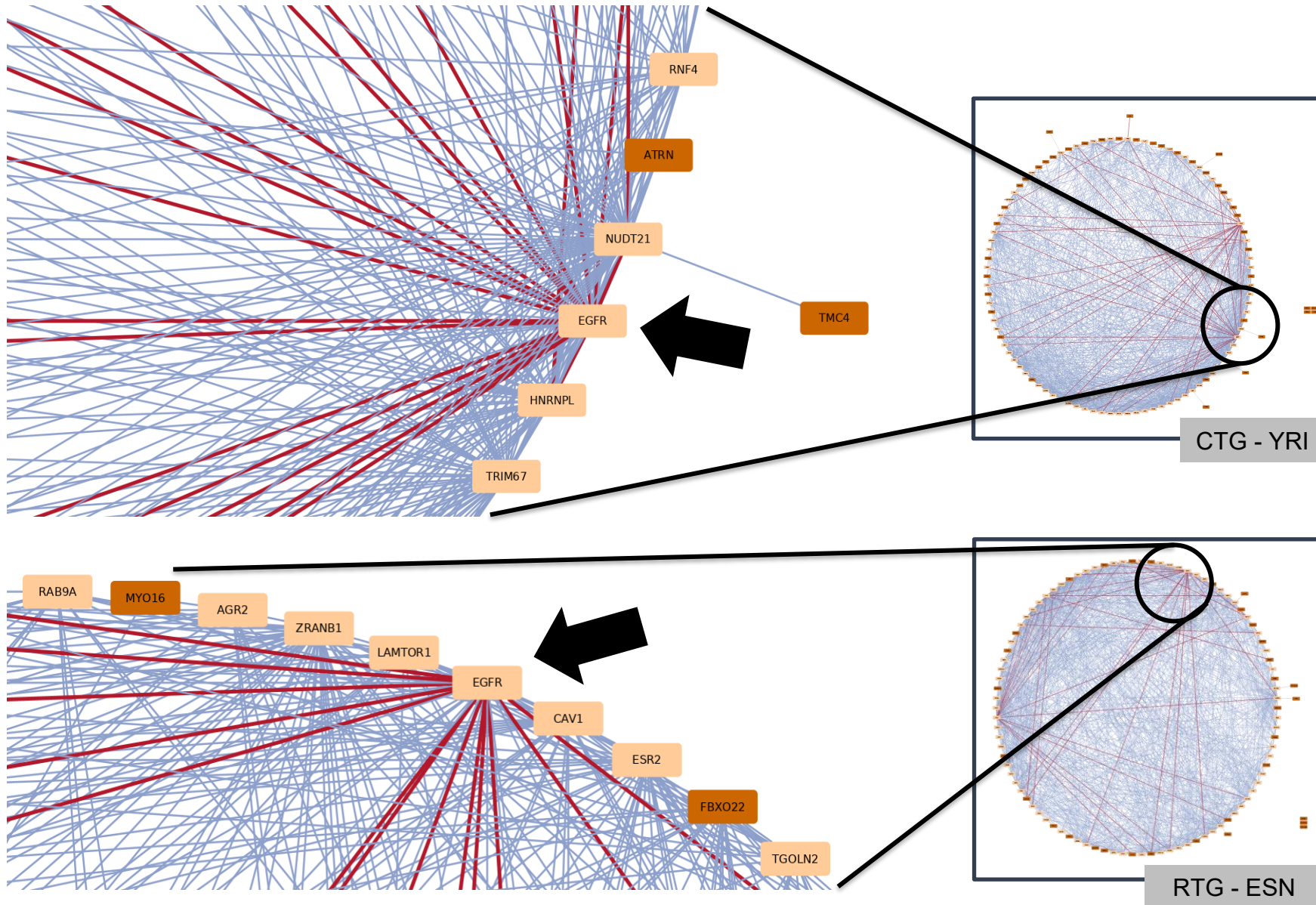
- Significant SNPs were mapped to genes, which were then used to build **interaction networks**.
- **Recruited genes** are genes directly connected to at least three input genes.





Recruitment of *EGFR* into Gene Interaction Networks from Additional Analyses

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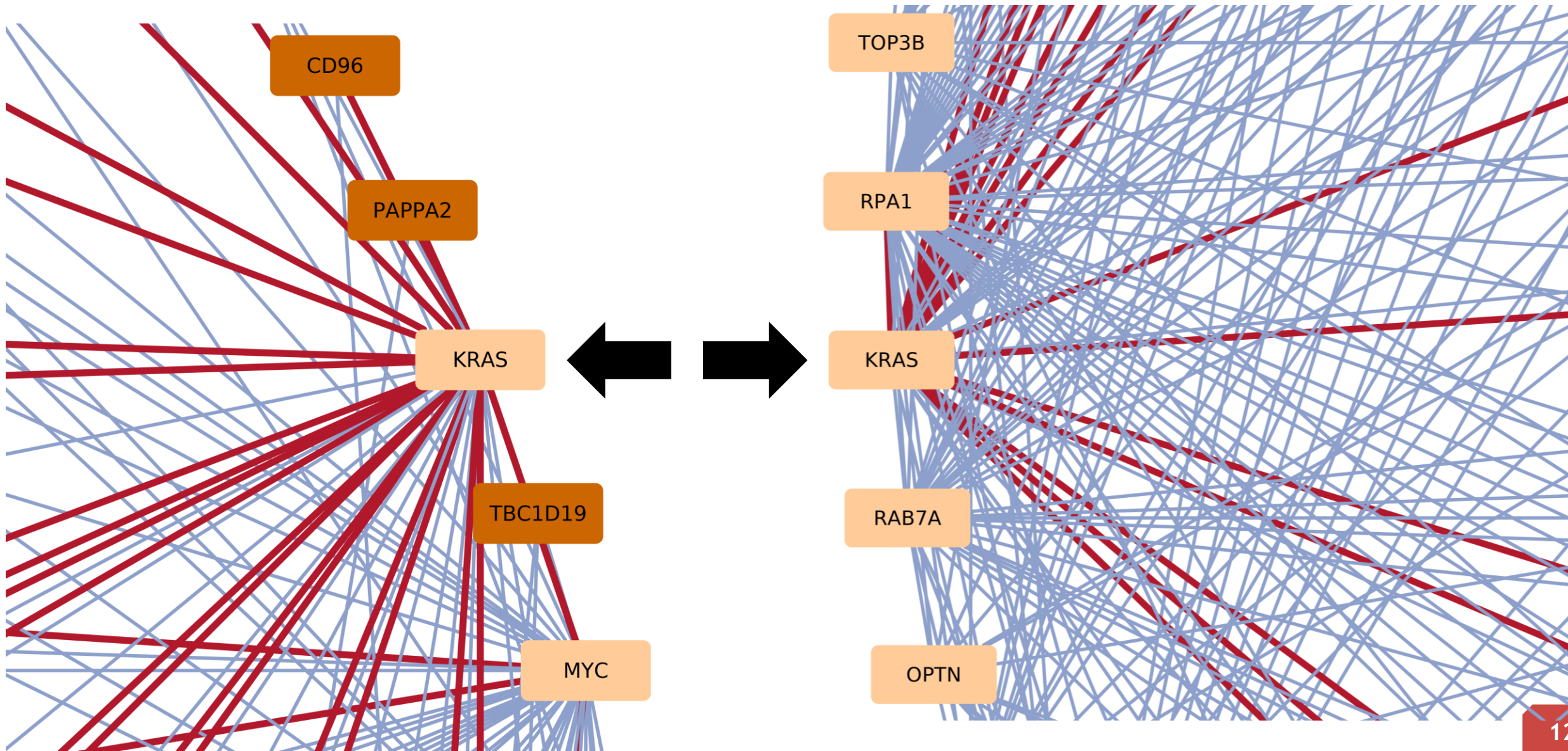


In addition to being a direct GWA - SNP hit, *EGFR* was independently recruited into two additional networks.



KRAS Identified as an Additional Highly Connected Hub Gene

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Comparison to Drosophila Genome Diversity Line Panel GWA Analysis upon Cadmium Exposure

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Drosophila melanogaster

Cadmium GWA -> gene network

Egfr

Genes directly connected to fly Egfr

Fmr1

Shrm

Pp1-87B

Ras85D

Conserved gene of interest



Human lymphoblastoid cell lines

GWA / network recovery

EGFR

Human ortholog

FXR2

SHROOM3

PPP1CC

KRAS

Recovered in

1 GWA
CTG-ESN

1 GWA
RTG-ESN

1 GWA
CTG-YRI

2 Networks
CTG-YRI RTG-ESN



PrecisionTox Data Explorer Finds the EGFR Connection

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PTox/DEX | PrecisionTox Data Explorer

DataDownloads

TranscriptomicsMetabolomicsChemicalsOrthologsFunctions

Explore DataGene Centric ViewCompare Data

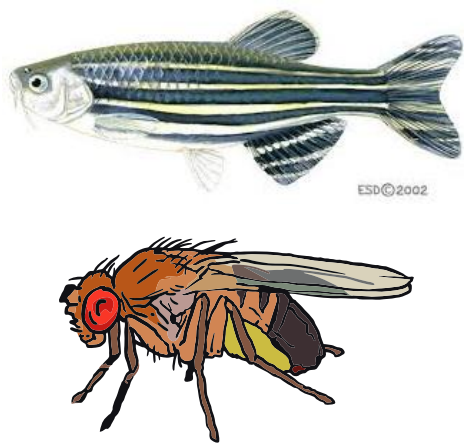
Choose an organism to search genes from:

Drosophila melanogaster

Search for a gene:

Egfr | Epidermal growth factor receptor (Egfr) (receptor) (Protein torpedo) | FBgn0003731

Submit



Exposure to Cadmium is the most significant inducer of fruit fly and zebrafish EGFR gene!

Expression tables

Show 50 entries CSV Excel Print Copy

Organism

Gene

Chemical

Dose

Timepoint (hrs)

log2FoldChange

log2FoldChange_SE

pvalue

padj

All

All

All

All

All

All

All

All

All

Danio rerio	LL0000009753	Cadmium chloride	BMD10	48	0.59	0.14	0	0
Drosophila melanogaster	Dmel_CG10079	Cadmium chloride	BMD10	24	0.43	0.1	0	0
Drosophila melanogaster	Dmel_CG10079	Cadmium chloride	BMD25	24	0.49	0.13	0	0
Drosophila melanogaster	Dmel_CG10079	DMSO	BMD25	4	-0.56	0.15	0	0
Drosophila melanogaster	Dmel_CG10079	DMSO	BMD25	6	-0.56	0.15	0	0
Homo sapiens	ERBB2	WY-14643 / Pirinixic acid	BMD10	48	-0.72	0.14	0	0
Homo sapiens	ERBB2	WY-14643 / Pirinixic acid	BMD25	24	-0.61	0.16	0	0
Homo sapiens	ERBB2	WY-14643 / Pirinixic acid	BMD25	24	-0.61	0.16	0	0
Homo sapiens	ERBB3	WY-14643 / Pirinixic acid	BMD25	48	0.78	0.13	0	0



PTox/DEX | PrecisionTox Data Explorer

Transcriptomics

Metabolomics

Chemicals

Orthologs

Functions

Explore Data

Gene Centric View

Compare Data

Choose organisms to compare:

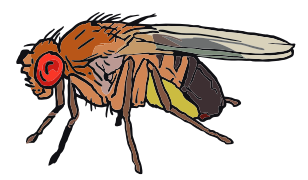
Danio rerio

Drosophila melanogaster

Homo sapiens

Choose chemical:

Cadmium chloride



Namespace: AOP						
Path/Term	Name	Direction	Ratio	Fisher-pv	Fisher-C-pv	Genes
Event:1521	Decrease, Growth	ENRICHED	27.617	4.6x10 ⁻¹⁰	6.3x10 ⁻⁰⁸	MT1A (1.00) MT1B (0.50) MT1E (1.00) MT1F (0.50) MT1G (1.00) MT1H (0.50) MT1X (0.50) MT2A (1.00)
Event:216	Decreased, PCK1 expression (control point for glycolysis/gluconeogenesis pathway)	ENRICHED	24.366	6.4x10 ⁻⁰⁹	8.8x10 ⁻⁰⁷	GCK (0.50) LDHA (1.00) LDHAL6A (0.50) LDHAL6B (1.00) LDHC (0.50) PCK1 (0.50) PGAM1 (1.00) PGAM4
Event:1512	Unfolded Protein Response	ENRICHED	7.446	6.0x10 ⁻⁰⁵	0.008	DNAJB1 (1.00) DNAJB4 (0.50) DNAJB5 (1.00) HSPA1B (1.00) HSPA1L (0.50) HSPA6 (1.00)
Event:1439	Systemic acute phase response	ENRICHED	8.668	6.3x10 ⁻⁰⁵	0.009	CCN1 (0.50) COMP (1.00) THBS1 (0.50) THBS2 (1.00) THBS3 (0.50) THBS4 (1.00)
Event:1605	Accumulation of misfolded proteins	ENRICHED	22.151	1.5x10 ⁻⁰⁴	0.021	HSPA1B (1.00) HSPA1L (0.50) HSPA6 (1.00)



- Significant response differences were observed between human populations and individual cell lines
- Minimal sex effects in cell lines
- GWAS for cadmium chloride identified gene networks linked to EFGR and KRAS signalling in humans
- Similar links to EFGR - KRAS signalling networks were discovered in fruit fly and in zebrafish
- Genetic variation in humans as well as in flies impacts toxic responses and should be considered in toxicity evaluations
- Next steps; Expression-QTL analysis will be carried out to further characterize SNP - gene interactions



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misvik biology



Maria E. Adonay, Robert Anholt, Trudy Mackay, Elisa Howansky and Katelynne Collins



Thank
you!

John Colbourne

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